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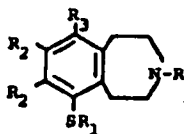
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**2,3,4,5-Tetrahydro-1H-3-Benzazepines, process for their production and pharmaceutical compositions having dopamine receptor blocking activity.**

**2,3,4,5-Tetrahydro-1H-3-benzazepines represented by the formula:**



or a nontoxic pharmaceutically acceptable acid addition salt thereof,  
process for their production and pharmaceutical compositions having dopamine receptor blocking activity.

wherein:

R is methyl, ethyl, dimethylallyl, phenethyl, cyclopropyl-methyl or 3-hydroxyethyl;

R<sub>1</sub> is phenyl, m- or p-substituted phenyl with the substituent being trifluoromethyl, chloro, methoxy, methyl, fluoro, nitro or hydroxy, cyclohexyl, thienyl, thienylmethyl, furyl or furylmethyl;

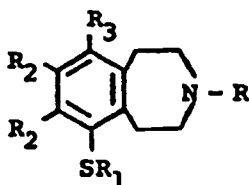
R<sub>2</sub> is hydrogen, methoxy, alkanoyloxy with the alkanoyl moiety having from 2 to 6 carbon atoms, or hydroxy, each R<sub>2</sub> being the same or different except that when one of R<sub>2</sub> is alkanoyloxy the other is hydrogen, methoxy or alkanoyloxy; and

R<sub>3</sub> is hydrogen, chloro, bromo, trifluoromethyl, fluoro or methyl,

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This invention relates to novel mercapto substituted-2,3,4,5-tetrahydro-1H-3-benzazepines having pharmacodynamic activity. More specifically the compounds of this invention have dopamine receptor blocking activity and therefore are useful as antipsychotic and antiemetic agents. The antipsychotic activity is similar to that of chlorpromazine.

The compounds of this invention are represented by the following general structural formula:



FORMULA I

wherein:

R represents methyl, allyl, dimethylallyl, phenethyl, cyclopropylmethyl or β-hydroxyethyl;

R<sub>1</sub> represents phenyl, m- or p-substituted phenyl with the substituent being trifluoromethyl, chloro, methoxy, methyl, fluoro, nitro or hydroxy, cyclohexyl, thienyl, thienylmethyl, furyl or furylmethyl;

1  $R_2$  represents hydrogen, methoxy, alkanoyloxy with the alkanoyl moiety having from 2 to 6 carbon atoms, or hydroxy, each  $R_2$  being the same or different except that when one of  $R_2$  is alkanoyloxy the other is hydrogen, 5 methoxy or alkanoyloxy; and

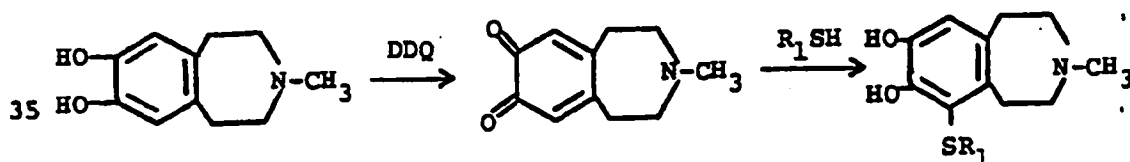
$R_3$  represents hydrogen, chloro, bromo, trifluoromethyl, fluoro or methyl.

Particular compounds of this invention represented by formula I above are when R is methyl,  $R_1$  is phenyl, 10 p-trifluoromethylphenyl, p-chlorophenyl, p-tolyl, p-fluorophenyl, cyclohexyl or 2-thienyl, both  $R_2$  are hydrogen, acetoxy or hydroxy, or one  $R_2$  is hydroxy and the other is methoxy, and  $R_3$  is hydrogen, chloro or bromo.

The pharmaceutically acceptable acid addition salts 15 having the utility of the free bases of Formula I, prepared by methods well known to the art, are formed with both inorganic or organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, pro- 20 pionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

U. S. Patents 3,671,519 and 3,483,185 name 25 "2,3,4,5-tetrahydro-8-methylmercapto-1H-3-benzazepine" as a starting material, however neither of these or equivalent prior art discloses the mercapto substituents of formula I above in a 3-benzazepine series.

The compounds of formula I wherein both  $R_2$  are 30 hydroxy are conveniently prepared from dihydroxy substituted benzazepines as shown in the following scheme:



1 in which  $R_1$  is as described above (except for hydroxy  
substituted phenyl). Thus, a 7,8-dihydroxy substituted  
benzazepine is oxidized, preferably with 2,3-dichloro-5,6-  
5 dicyano-1,4-benzoquinone (DDQ) in an inert organic solvent  
in which the reactants are soluble such as methanol or  
ethanol, with chilling at about 0-5°C. or at ambient  
temperature until the oxidation is complete. A number of  
other mild oxidizing agents known to convert catechols to  
10 o-quinones may be employed such as, for example, silver  
oxide, ceric ammonium nitrate, chloranil or silver  
carbonate. The 7,8-dione intermediate is then reacted with  
the desired mercaptan ( $R_1SH$ ) in a suitable inert organic  
solvent such as an alcoholic solvent, methanol or ethanol,  
at about ambient temperature to give the mercapto  
15 substituted product. The hydroxy substituted phenyl  
products are conveniently obtained from the corresponding  
methoxy substituted phenyl compounds by treatment with, for  
example, boron tribromide.

20 Alternatively the above dihydroxy substituted  
benzazepine starting material, or its dimethyl ether  
derivative, is brominated to give the 6-bromo compound which  
is reacted with n-butyl lithium and then an appropriate  
disulfide to give the 6-thio substituted product. The ether  
groups can be cleaved to hydroxy groups by treatment with  
25 48% hydrobromic acid.

The quinone intermediate shown in the above reac-  
tion scheme clearly is a valuable intermediate and as such  
forms a part of this invention.

30 The methoxy or alkanoyloxy derivatives of formula I  
( $R_2$ ) are prepared by alkylation-acylation methods which  
are conventional to the art. For example, reaction of the  
7,8-dihydroxy product obtained as above with diazomethane  
gives the dimethoxy derivative and with acetyl bromide in  
triethylamine gives the diacetoxy derivative. Selective  
35 demethylation of a 7,8-dimethoxy derivative with, for  
example, methionine in methanesulfonic acid gives the mixed  
hydroxy/methoxy products.

1 To prepare the 7,8-dihydroxy compounds of formula I  
 wherein  $R_3$  is chlorine or bromine, the catechol product  
 prepared above is oxidized with DDQ followed by reaction  
 with hydrogen chloride or hydrogen bromide in methanolic  
 5 solution. Alternatively a chloro or bromo substituted  
 3-benzazepine may be employed as a suitable starting  
 material. Thus, for example, 3-methyl-7,8-dimethoxy-3-  
 benzazepine is brominated to give the 6,9-dibromo derivative  
 which is reacted with n-butyl lithium followed by the appro-  
 10 priately substituted disulfide to give the 6-thio substi-  
 tuted-9-bromo product. The dimethoxy groups can be cleaved  
 with for example methionine in methanesulfonic acid.

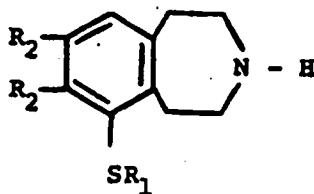
Further, a convenient method of preparation for a  
 6-chloro catechol product employs an N-protected-7,8-di-  
 15 methoxy-3-benzazepine as a starting material. For example,  
 N-carboethoxy-7,8-dimethoxy-3-benzazepine is reacted with a  
 sulfenyl chloride under Friedel-Crafts reaction conditions  
 to introduce the 6-phenylthio group and the carboethoxy  
 group is then reduced to methyl with an alkali metal  
 20 hydride, for example lithium aluminum hydride. The  
 6-phenylthio group is oxidized with for example periodate to  
 a phenylsulfinyl group and this compound is treated with  
 thionyl chloride to simultaneously introduce the 9-chloro  
 group and reduce the phenylsulfinyl to phenylthio. If  
 25 desired, the dimethoxy groups can be cleaved with, for  
 example, methionine in methanesulfonic acid.

The 7,8-dihydroxy compounds of formula I wherein  
 $R_3$  is trifluoromethyl are prepared by reacting the  
 corresponding 9-bromo substituted catechol with acetic  
 30 anhydride to give the 7,8-diacetoxy derivative and treating  
 this with trifluoromethyl iodide in the presence of copper  
 powder in dimethylformamide to give the trifluoromethyl sub-  
 stituted compound, optionally followed by acid hydrolysis  
 with dilute aqueous hydrochloric acid to obtain the unpro-  
 35 tected derivatives. Similarly a 9-bromo-7,8-dimethoxy com-

1 pound of formula I can be converted to the corresponding  
9-methyl product via conversion to the 9-carboxaldehyde,  
reduction to hydroxymethyl and hydrochloric acid treatment  
to give the chloromethyl derivative which is then reduced to  
5 methyl.

The compounds of formula I wherein  $R_2$  and  $R_3$   
are all hydrogen are conveniently prepared from a halo, such  
as bromo or chloro, substituted benzazepine by reaction with  
for example n-butyl lithium followed by the appropriately  
10 substituted disulfide. Introduction of an  $R_3$  substituent  
other than hydrogen is accomplished for example by nitration  
of a chloro substituted benzazepine, displacement of the  
chlorine by the appropriately substituted mercaptan, follow-  
ed by reduction of the nitro group, subsequent diazotiza-  
15 tion of the amine and conversion of the diazonium salt to  
the appropriate  $R_3$  substituted derivative. Similarly  
compounds of formula I wherein one  $R_2$  is hydroxy and  $R_3$   
is hydrogen are obtained from the above described amino  
substituted benzazepine by diazotization followed by  
20 treatment with aqueous sulfuric acid. It will be obvious to  
one skilled in the art that other combinations of these  
basic reactions will give compounds of formula I wherein one  
 $R_2$  is hydroxy and  $R_3$  is other than hydrogen, as  
illustrated in the examples below.

25 The substituent R of the compounds of formula I can  
be conveniently introduced by reaction with a corresponding  
N-unsubstituted derivative, for example as shown by the  
following formula:



1 wherein R<sub>1</sub> is phenyl and R<sub>2</sub> is hydroxy or methoxy. Thus  
the N-unsubstituted derivative is alkylated or acylated as  
appropriate to obtain the R substituted products of formula  
I. The N-unsubstituted derivatives are clearly valuable  
5 intermediates, forming a part of this invention, and can be  
prepared by methods described above for example via the  
dione or by bromination followed by introduction of the  
6-thio substituent through a lithium intermediate.

The dopamine receptor blocking activity of the com-  
10 pounds of this invention is demonstrated by antagonism of  
avoidance acquisition in rats and/or block of the effects of  
dopamine on dopamine sensitive adenylate cyclase in rat  
striatal homogenate. Central dopamine receptor blocking  
activity is a measure of potential antipsychotic activity.  
15 In the pharmacological procedure used to measure antagonism  
of avoidance acquisition, naive male rats are given either a  
test compound or saline at a suitable time period prior to  
testing. The rats are then placed in a dark soundproof box  
with a grid floor through which footshock is delivered.  
20 Trials begin at 30-second intervals. The beginning of each  
trial is signaled by a light and a buzzer which continues  
for 10 seconds, at which time footshock is added for an  
additional 15 seconds. In each trial a single lever press  
by the animal terminates the sequence. Evaluation of drug  
25 activity is based on the number of trials in which the  
animals fail to avoid or fail to escape footshock during the  
last 40 trials of a 100 trial, 50-minute session. The  
ED<sub>50</sub> is defined as that dose of drug calculated to reduce  
the number of avoidance responses during the last 40 trials  
30 to 50% of the (pooled) control value.

As an example of the antipsychotic activity of the  
compounds of formula I, the ED<sub>50</sub> values in mg/kg, i.p.  
obtained from testing the indicated compounds in the above  
procedure are as follows:

35

- 1 7,8-dihydroxy-3-methyl-6-phenylthio-  
2,3,4,5-tetrahydro-1H-3-benzazepine,  
ED<sub>50</sub> 0.5;  
6-cyclohexylthio-7,8-dihydroxy-3-methyl-  
2,3,4,5-tetrahydro-1H-3-benzazepine,  
ED<sub>50</sub> 1.0;
- 5 9-chloro-7,8-dihydroxy-3-methyl-6-phenylthio-  
2,3,4,5-tetrahydro-1H-3-benzazepine,  
ED<sub>50</sub> 0.08;  
7,8-dihydroxy-3-methyl-6-(p-trifluoromethylphenyl-  
thio)-2,3,4,5-tetrahydro-1H-3-benzazepine, ED<sub>50</sub>  
1.6;  
3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine, ED<sub>50</sub> 1.6;
- 10 7,8-dihydroxy-3-methyl-6-(2-thienylthio)-  
2,3,4,5-tetrahydro-1H-3-benzazepine,  
ED<sub>50</sub> 0.14;  
8-hydroxy-7-methoxy-3-methyl-6-phenylthio-  
2,3,4,5-tetrahydro-1H-3-benzazepine,  
ED<sub>50</sub> 0.26;  
7,8-dihydroxy-6-(p-fluorophenylthio)-3-methyl-  
2,3,4,5-tetrahydro-1H-3-benzazepine, ED<sub>50</sub> 0.18;
- 15 7,8-dihydroxy-3-methyl-6-(p-tolylthio)-2,3,4,5-  
tetrahydro-1H-3-benzazepine, ED<sub>50</sub> 1.2;  
9-bromo-7,8-dihydroxy-3-methyl-6-phenylthio-  
2,3,4,5-tetrahydro-1H-3-benzazepine, ED<sub>50</sub> 0.18  
and  
7,8-dihydroxy-6-furfurylthio-3-methyl-2,3,4,5-  
1H-3-benzazepine, ED<sub>50</sub> 1.2.
- 20

For comparison, chlorpromazine has an Avoidance ED<sub>50</sub> of  
1.5 mg/kg, i.p.

The compounds of formula I wherein both R<sub>2</sub> are  
hydroxy (catechols) have antiemetic activity as demonstra-  
25 ted by anti-apomorphine activity in dogs. In this pharma-  
cological procedure, a test compound is administered sub-  
cutaneously to one or more groups of test animals  
(pre-selected for their sensitivity to apomorphine) while  
another group serves as controls. After a suitable pre-  
30 treatment time, apomorphine hydrochloride is administered  
to each animal in a dosage of 0.1 mg/kg, s.c. Frequency  
of emesis is observed and recorded over the next 40  
minutes. The mean frequency of emesis is calculated for  
each test group and compared with the controls. Final  
35 results are reported as a percentage change in emetic



1 frequency of the test animals relative to the controls. A  
test compound is considered active if it produces at least  
a 20% change in emetic frequency of the test animals from  
that of the controls. The catechols have antiemetic  
5 ED<sub>50</sub> values (that is, reduce emetic frequency by 50%  
over controls) of less than 1 mg/kg, s.c.

The compounds of this invention may be admini-  
stered as pharmaceutical compositions in conventional  
dosage unit forms. These compositions which form a part  
10 of this invention are prepared by incorporating a compound  
of formula I, or a pharmaceutically acceptable acid  
addition salt thereof, in a nontoxic amount sufficient to  
produce dopamine receptor blocking activity in an animal  
or human subject, with a nontoxic pharmaceutical carrier  
15 according to accepted procedures. Preferably the composi-  
tions will contain the active ingredient in an active but  
nontoxic amount selected from about 1 mg. to about 300 mg.  
of active ingredient per dosage unit.

The pharmaceutical carrier employed may be, for  
20 example, either a solid or liquid, giving rise to a wide  
variety of pharmaceutical forms. If a solid pharmaceuti-  
cal carrier is used, such as lactose, magnesium stearate,  
terra alba, sucrose, talc, stearic acid, gelatin, agar,  
pectin, acacia and the like, the composition can be  
25 tableted, used as a pharmaceutical powder, placed in a  
hard gelatin capsule or in the form of a troche or  
lozenge. The amount of solid carrier will vary widely but  
preferably will be from about 25 mg. to about 1 g. If a  
liquid pharmaceutical carrier is used, such as syrup,  
30 peanut oil, olive oil, sesame oil, water and the like, the  
composition will be in the form of a soft gelatin capsule,  
syrup, emulsion or a liquid suspension. Similarly the  
carrier or diluent may include a time delay material such  
as glyceryl monostearate or glyceryl distearate alone or  
35 with a wax.

1           Parenteral dosage forms such as for intramuscular  
administration are obtained by dissolving a water soluble  
salt of the active medicament in water or saline solution  
in a concentration such that 1 ml. of the solution con-  
5   tains from about 2 mg. to about 50 mg. of active ingre-  
dient. The solution can then be filled into single ampuls  
or multiple dose vials.

          The pharmaceutical preparations are made follow-  
ing the conventional techniques of the pharmaceutical  
10 chemist involving mixing, granulating and compressing when  
necessary, or variously mixing and dissolving the ingre-  
dients as appropriate to give the desired end product.

          To produce dopamine receptor blocking activity, a  
compound of formula I or a pharmaceutically acceptable  
15 acid addition salt thereof, usually combined with a  
pharmaceutical carrier, is administered internally to an  
animal or human subject in need of such activity in a non-  
toxic amount sufficient to produce said activity. The  
route of administration may be oral or parenteral. Advan-  
20 tageously equal doses will be administered until a desired  
effect is obtained, for example two or three times a day,  
with the daily dosage regimen being selected from about 2  
mg. to about 900 mg. of active ingredient.

          The following examples illustrate the preparation  
25 of specific compounds and pharmaceutical compositions of  
this invention and as such are not to be construed as  
limitations thereof. Those skilled in the art will appre-  
ciate that other modifications of the synthetic procedures  
described and the use of alternative starting materials  
30 may also be employed to prepare the compounds of formula I.

EXAMPLE 1

          To a cooled solution of aminoacetaldehyde  
dimethylacetal (21 g., 0.2 mole) and dicyclohexylcarbo-  
dimide (42.5 g., 0.205 mole) in 500 ml. of methylene  
35 chloride was added homoveratric acid (39.2 g., 0.2 mole)

1 portionwise with cooling and stirring. After the addition  
was completed, the reaction mixture was stirred at room  
temperature for 1/2 hour, kept in refrigerator overnight  
and filtered. The filtrate was evaporated to dryness to  
5 give an oil which was chilled to form the solid  
N-(2,2-dimethoxyethyl)-3,4-dimethoxyphenylacetamide, m.p.  
60-63°C.

The acetamide (40 g.) was mixed with 200 ml. of  
concentrated hydrochloric acid and 200 ml. of glacial  
10 acetic acid and allowed to stand at room temperature over-  
night. The reaction mixture was poured into ice/water and  
the resulting solid was washed with water/methanol to give  
2,3-dihydro-7,8-dimethoxy-2-oxo-1H-3-benzazepine,  
m.p. 239-241°C.

15 The benzazepine (12 g.) was dissolved in 120-130  
ml. of glacial acetic acid by heating and then poured into  
a Parr bottle. To the solution was added 0.8 g. of 10%  
palladium-on-carbon and the mixture was hydrogenated for 1  
to 1½ hours. The catalyst was filtered off and the fil-  
20 trate was evaporated to dryness to give the 7,8-di-  
methoxy-2-oxo-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p.  
190-192°C.

To a suspension of the tetrahydrobenzazepine (22  
g., 0.1 mole) in 250 ml. of dry tetrahydrofuran was added  
25 225 ml. of 0.94 M diborane, slowly. After addition was  
completed the mixture was refluxed for 1 hour, cooled,  
dilute hydrochloric acid added and then heated on a steam  
bath for 30-40 minutes. The residue was diluted with  
water, made basic with 10% sodium hydroxide solution and  
30 extracted with ethyl acetate. The dried extract was  
evaporated and the solid was converted to its hydro-  
chloride salt, 7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-  
benzazepine hydrochloride, m.p. 240-241°C.

The tetrahydrobenzazepine (12.3 g) was mixed with  
35 200 ml. of 48% hydrobromic acid and refluxed for 1-2

1 hours. The reaction mixture was evaporated to dryness and azeotroped with toluene to yield 7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide, m.p. 278-280°C.

To 300 ml. of a methanolic solution of the  
5 dihydroxybenzazepine hydrobromide (9.7 g) was added a slight molar excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, portionwise under nitrogen. The mixture was stirred at room temperature for 1/2 hour, chilled in an ice bath and filtered to give 2,3,4,5-tetrahydro-1H-3-  
10 benzazepine-7,8-dione hydrobromide.

To 500 ml. of a methanolic solution of thiophenol (6.4 g., 0.058 mole) was added the above dione hydrobromide, portionwise. The resulting solution was stirred at room temperature under nitrogen for 1 hour and then  
15 evaporated to dryness. The residual oil was stirred with ether and triturated with ethanol to furnish 7,8-dihydroxy-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide, m.p. 125-128°C. This catechol can be converted to 3-substituted products of formula I.

20

#### EXAMPLE 2

A mixture of 7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (19.5 g., 0.094 mole), 78 ml. of 37% formaldehyde and 117 ml. of 99-100% formic acid was refluxed overnight and then evaporated to dryness. Dilute  
25 hydrochloric acid (140 ml.) was added to the resulting residue and evaporated to dryness again. This residue was treated with 140 ml. of 10% sodium hydroxide solution and extracted with ethyl acetate. The extract was washed, dried and the residue converted to its hydrochloride salt  
30 to give 7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, m.p. 250-254°C.

The above 3-methylbenzazepine (5.2 g., 0.02 mole) was mixed with 100 ml. of 48% hydrobromic acid and refluxed for 1 to 1½ hours. The reaction mixture was  
35 evaporated to dryness and azeotroped with toluene to leave 7,8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide, m.p. 230-233°C. (decomp.).

1 To a solution of 16 g. (0.0584 mole) of the  
dihydroxybenzazepine in 300 ml. of methanol was added,  
portionwise, 14.3 g. (0.063 mole) of 2,3-dichloro-5,6-  
dicyano-1,4-benzoquinone under nitrogen and the mixture  
5 stirred at room temperature for 1 hour. The reaction mix-  
ture was chilled in an ice-bath and filtered to give  
3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-dione  
hydrobromide.

To a methanolic solution (200 ml.) of thiophenol  
10 (1.92 g., 0.0175 mole) was added 2.2 g. (0.0081 mole) of  
the above dione portionwise and the resulting solution was  
stirred at room temperature under nitrogen for 1 hour.  
The reaction mixture was evaporated to leave 7,8-dihydroxy-  
3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine  
15 hydrobromide, m.p. 116-120°C.; free base m.p. 174°C.

Following the above procedure and reacting the  
dione with cyclohexylmercaptan, m-trifluoromethylthio-  
phenol, p-trifluoromethylthiophenol or p-chlorothiophenol  
yielded the respective products: 6-cyclohexylthio-7,8-di-  
20 hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p.  
148-157°C.; 7,8-dihydroxy-3-methyl-6-(m-trifluoro-  
methylphenylthio)-2,3,4,5-tetrahydro-1H-3-benzazepine,  
m.p. 183-185°C.; 7,8-dihydroxy-3-methyl-6-(p-trifluoro-  
methylphenylthio)-2,3,4,5-tetrahydro-1H-3-benzazepine  
25 fumarate m.p. 222°C.; and 6-(p-chlorophenylthio)-7,8-di-  
hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine,  
hemifumarate m.p. 209-211°C.

### EXAMPLE 3

To a methanolic suspension of 7,8-dihydroxy-3-  
30 methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine  
(1.0 g., 0.0033 mole) was added, portionwise, diazomethane  
generated in the conventional way using N-methyl-N'-  
nitro-N-nitrosoguanidine. The mixture was stirred at room  
temperature for 1 hour, excess diazomethane was removed  
35 under a stream of nitrogen and then concentrated. Fumaric

- 1 acid dissolved in a minimum amount of methanol was added  
and the solution chilled to give 7,8-dimethoxy-3-methyl-6-  
phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine fumarate,  
m.p. 181-184°C.

5

EXAMPLE 4

- A solution of 3.2 g. of 7,8-dihydroxy-3-methyl-6-  
phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine in about  
500 ml. of dry benzene was stirred at room temperature for  
15 minutes and then 4.5 ml. of triethylamine was added.  
10 Acetyl bromide (5.4 g., 0.044 mole) in 20 ml. of benzene  
was added dropwise and the mixture refluxed for 1½  
hours. The reaction mixture was evaporated to dryness and  
the residue partitioned between 5% sodium bicarbonate  
solution and ethyl acetate. The ethyl acetate solution  
15 was washed, dried and evaporated. The residue was treated  
with fumaric acid to yield 7,8-diacetoxy-3-methyl-6-  
phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine fumarate,  
m.p. 156-161°C.

- Similarly 6-cyclohexylthio-7,8-dihydroxy-3-  
20 methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was reacted  
with acetyl bromide as described above to give 7,8-di-  
acetoxy-6-cyclohexylthio-3-methyl-2,3,4,5-tetrahydro-1H-3-  
benzazepine; hydrobromide salt m.p. 149-150°C.

EXAMPLE 5

- 25 To a mixture of 7 g. (0.0337 mole) of  
7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine  
dissolved in 170 ml. of acetonitrile and 5 ml. of  
triethylamine, cooled in an ice bath, was added 4.25 g.  
(0.035 mole) of allyl bromide in 30 ml. of acetonitrile,  
30 dropwise with stirring. The mixture was brought to room  
temperature and refluxed for 1½ hours. The reaction  
mixture was evaporated to dryness, partitioned between  
ethyl acetate and 5% sodium bicarbonate solution, and the  
separated ethyl acetate dried and evaporated to give  
35 3-allyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine.

1           The 3-allyl benzazepine (4.5 g., 0.0182 mole) was  
dissolved in 200 ml. of methylene chloride, cooled and 9  
g. (0.036 mole) of boron tribromide in 45 ml. of methylene  
chloride was added dropwise. The mixture was stirred in  
5 the ice bath for 30 minutes and then at room temperature  
for 1 hour. Excess boron tribromide was destroyed by  
adding methanol and the mixture evaporated to dryness.  
The residue was triturated with acetonitrile to yield  
3-allyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine  
10 hydrobromide, m.p. 195-204°C.

Following the procedures outlined in Example 2  
the 3-allyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-  
benzazepine hydrobromide was treated with  
2,3-dichloro-5,6-dicyano-1,4-benzoquinone to give the  
15 7,8-dione which was then reacted with, for example,  
thiophenol to obtain the corresponding 3-allyl-7,8-  
dihydroxy-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine  
hydrobromide, m.p. 103-123°C.

Similarly, reaction of dimethylallyl bromide as  
20 described above gives as the final product 7,8-dihydroxy-  
3-dimethylallyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benza-  
zepine hydrobromide.

#### EXAMPLE 6

A solution of 5 g. (0.0166 mole) of 7,8-dihydroxy-  
25 3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine  
in 250 ml. of methanol was acidified with ethereal hydro-  
gen chloride to yield the hydrochloride salt. The latter  
was dissolved in 300 ml. of methanol and 4.0 g. (0.0176  
mole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was  
30 added portionwise under nitrogen and the mixture stirred  
at room temperature for 20 minutes. Ether was added to  
the reaction mixture and the solvents decanted to leave  
3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzaze-  
pine-7,8-dione hydrochloride. This hydrochloride was  
35 dissolved in a minimum amount of methanol and then added

1 to a methanolic hydrogen chloride solution, portion-  
wise. The mixture was stirred at room temperature for 1  
hour, the solvent was evaporated and the residue tri-  
5 fied via conversion to its free base to give 9-chloro-  
7,8-dihydroxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-  
1H-3-benzazepine, m.p. 173-174°C.

EXAMPLE 7

To a stirred solution of 2-thiophenethiol (0.9  
10 g., 0.0076 mole) in 200 ml. of methanol was added  
portionwise 2 g. (0.0074 mole) of 3-methyl-2,3,4,5-tetra-  
hydro-1H-3-benzazepine-7,8-dione, at room temperature  
under argon. After stirring for 1 hour, the methanol was  
distilled under vacuum, the residue slurried in 30 ml. of  
15 water and filtered. The filtrate was made basic to give  
the product, 7,8-dihydroxy-3-methyl-6-(2-thienylthio)-  
2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 189-191°C.

Similarly the above dione (5 g., 0.018 mole) was  
added portionwise to a solution of 2.3 g. (0.02 mole) of  
20 3-thiophenethiol in 200 ml. of methanol to yield upon  
workup the corresponding product, 7,8-dihydroxy-3-methyl-  
6-(3-thienylthio)-2,3,4,5-tetrahydro-1H-3-benzazepine,  
m.p. 189-191°C.

EXAMPLE 8

25 A stirred solution of 620 ml. of 0.9 M *n*-butyl  
lithium (0.56 mole) in tetrahydrofuran is placed under  
nitrogen and cooled to -70°C. To this stirred solution  
is added dropwise, during a period of 30 minutes, a solu-  
tion of 0.1 mole of 6-bromo-3-methyl-2,3,4,5-tetra-  
30 hydro-1H-3-benzazepine in 230 ml. of tetrahydrofuran. The  
solution is stirred at -70°C for 30 minutes and then a  
solution of 135 g. (0.62 mole) of diphenyldisulfide in 385  
ml. of tetrahydrofuran is added dropwise. Stirring at  
-70°C. is continued for 1 hour. The nearly colorless  
35 solution is poured slowly with stirring into 5 l. of



1 ice/water containing excess hydrochloric acid. The mixture is extracted with ether, then the aqueous phase is made alkaline by addition of 10 N sodium hydroxide. An ether extract of the resulting mixture is washed with a  
5 saturated solution of sodium chloride, dried over magnesium sulfate and concentrated. The residual liquid is subjected to chromatographic separation to afford 3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine, which is converted to a cyclohexylsulfamic acid  
10 salt in methanol-ether, m.p. 136-139°C.

EXAMPLE 9

To a stirred mixture of 400 g. of concentrated sulfuric acid and 100 g. of concentrated nitric acid at 0-5°C. is added, in portions, 19.6 g. (0.1 mole) of  
15 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine. The solution is stirred at 0-5°C. for 2.5 hours, then it is poured cautiously into 1.5 liters of ice/water. The solution is made basic by addition of excess sodium hydroxide, then it is extracted with ether. After being  
20 washed several times with water the extract is dried and concentrated. The resulting mixture of approximately equal parts of 6-chloro-3-methyl-9-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine and 6-chloro-3-methyl-7-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine is separated by  
25 chromatographic methods.

To a stirred solution of 11.0 g. (0.1 mole) of thiophenol in 200 ml. of dimethylformamide at 0-10°C., under an atmosphere of nitrogen, is added cautiously, in portions, 4.65 g. (0.11 mole) of a 57% dispersion of  
30 sodium hydride in mineral oil. The resulting solution is stirred for 15 minutes at 25°C. and then a solution of 24.1 g. (0.1 mole) of 6-chloro-3-methyl-9-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine in 50 ml. of dimethylformamide is added dropwise. The reaction mixture is heated at  
35 100°C. for 2 hours, then it is cooled to 25°C. and

1 poured into ice/water. The resulting solid is filtered,  
air-dried and recrystallized from ethyl acetate-hexane to  
give 3-methyl-9-nitro-6-phenylthio-2,3,4,5-tetrahydro-1H-  
3-benzazepine.

5 To a solution of 15.7 g. (0.05 mole) of 3-methyl-  
9-nitro-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine  
in 350 ml. of ethanol and 125 ml. of water is added, in  
portions, 35 g. (0.2 mole) of sodium hydrosulfite. The  
mixture is stirred and refluxed for 16 hours, then an  
10 additional 52 g. (0.3 mole) of sodium hydrosulfite is  
added and refluxing is continued for 30 hours, allowing  
about one-half of the solvent to distill from the reaction  
during the last hour. The mixture is cooled, diluted with  
water, made alkaline with ammonium hydroxide and extracted  
15 with ethyl acetate. After being dried, the extract is  
concentrated to give 9-amino-3-methyl-6-phenylthio-  
2,3,4,5-tetrahydro-1H-3-benzazepine which is purified by  
chromatography. A solution of the base in ethanol is  
treated with an excess of hydrogen chloride. Following  
20 addition of ether crystalline 9-amino-3-methyl-6-phenyl-  
thio-2,3,4,5-tetrahydro-1H-3-benzazepine dihydrochloride  
is obtained.

Alternatively the 9-nitro compound is hydro-  
genated in ethanol solution with 5% palladium-on-carbon at  
25 50 p.s.i. for 2 hours to give the 9-amino derivative.

To a stirred suspension of 17.9 g. (0.05 mole) of  
9-amino-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine dihydrochloride in 50 ml. of water and 50 ml.  
of concentrated hydrochloric acid at 0-5°C. is added  
30 dropwise a solution of 4.2 g. (0.06 mole) of sodium  
nitrite in 25 ml. of water. After being stirred at  
0-5°C. for 30 minutes, the resulting diazonium solution  
is added to a solution of 6.0 g. (0.06 mole) of cuprous  
chloride in 25 ml. of concentrated hydrochloric acid. The  
35 mixture is stirred for 16 hours at 25°C., then it is

1 warmed to 60-80°C. for 1 hour. After being cooled to  
15-20°C., the mixture is made alkaline and extracted  
with ether. The ether extract is dried over magnesium  
sulfate and concentrated to leave 9-chloro-3-methyl-6-  
5 phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine which is  
purified by chromatography or by recrystallization of  
appropriate acid addition salts; hydrochloride salt m.p.  
231-232°C.

EXAMPLE 10

10 To a stirred solution of 114 ml. of water and 15  
ml. of concentrated sulfuric acid at 60-70°C. is added  
23.2 g. (0.082 mole) of 9-amino-3-methyl-6-phenylthio-  
2,3,4,5-tetrahydro-1H-3-benzazepine. The resulting  
suspension is stirred vigorously and cooled to 0-5°C.  
15 To this suspension is added 6.3 g. (0.091 mole) of sodium  
nitrite in 10 ml. of water at a rate such that the  
temperature does not exceed 5°C. The resulting  
diazonium solution is added dropwise to a boiling solution  
of 200 g. of cuprous sulfate and 300 ml. of water. After  
20 being refluxed for 15 minutes the solution is cooled, a  
trace of ascorbic acid is added and the pH is adjusted to  
7.0 with ammonium hydroxide. The mixture is extracted  
with ethyl acetate. After being dried the extract is  
concentrated to afford 9-hydroxy-3-methyl-6-phenyl-  
25 thio-2,3,4,5-tetrahydro-1H-3-benzazepine. Purification is  
accomplished by chromatography or by recrystallization of  
an appropriate acid addition salt.

EXAMPLE 11

Following the procedures outlined in Example 9,  
30 the isomeric 6-chloro-3-methyl-7-nitro-2,3,4,5-tetrahydro-  
1H-3-benzazepine is treated with sodium thiophenolate to  
give the 6-phenylthio intermediate and the nitro group is  
reduced with sodium hydrosulfite. To a solution of 2.6 g.  
(0.0125 mole) of the resulting 7-amino-3-methyl-6-phenyl-  
35 thio-2,3,4,5-tetrahydro-1H-3-benzazepine in 25 ml. of 3 N

1 sulfuric acid at 0-3°C., a solution of sodium nitrite  
(1 g. in 5 ml. of water) is added dropwise until a  
positive test for nitrous acid is obtained. Excess  
nitrous acid is decomposed by adding 0.2 to 0.3 g. of urea  
5 and stirring for 10 minutes. The diazonium solution is  
added dropwise with stirring to 200 ml. of 50% sulfuric  
acid at 70°C. and maintained at 70°C. until all of the  
diazonium salt is decomposed. On cooling the warm  
solution in an ice bath a crystalline precipitate is  
10 formed. After being chilled for 30 minutes at 0°C., the  
mixture is filtered. The solid is washed with a small  
volume of ice/water. Recrystallization affords  
7-hydroxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine sulfate.

15

EXAMPLE 12

A suspension of 12.0 g. (0.05 mole) of 6-chloro-  
3-methyl-9-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine, 100  
ml. of ethanol and 0.2 g. of platinum dioxide is hydro-  
genated on a Parr apparatus at 25°C. and an initial  
20 hydrogen pressure of 4.12 bar. After the rapid hydrogen  
uptake is completed, the mixture is filtered and the  
filtrate is concentrated in vacuo to give 9-amino-6-  
chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

A mixture of 10.5 g. (0.05 mole) of 9-amino-6-  
25 chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and 50  
ml. of acetic anhydride is stirred and heated at  
60-65°C. for 4 hours. The resulting solution is poured  
into ice/water and stirred at 25°C. for 16 hours, then  
it is made alkaline by addition of sodium hydroxide at  
30 5-10°C. The precipitate is immediately filtered to give  
9-acetamido-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-  
benzazepine.

To a stirred mixture of 200 g. of concentrated  
sulfuric acid and 50 g. of concentrated nitric acid at  
35 0-5°C. is added, in portions, 12.6 g. (0.05 mole) of

1 9-acetamido-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-  
benzazepine. The solution is stirred at 0-5°C. for 2  
hours and then it is poured cautiously into 500 ml. of  
ice/water. The solution is made alkaline with sodium  
5 hydroxide. After being stirred at 25°C. for 16 hours,  
the mixture is filtered to give 9-amino-6-chloro-3-  
methyl-8-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine.

A solution of 100 ml. of sulfuric acid and 50 ml.  
of water is cooled to -10°C. and maintained at this  
10 temperature while 3.7 g. (0.054 mole) of sodium nitrite is  
added in small portions over a period of about 15  
minutes. Cold 50% hypophosphorous acid 19.3 ml., (0.186  
mole) is added over a period of 10-15 minutes, the  
temperature still being maintained at -10°C. A solution  
15 of 5.1 g. (0.02 mole) of 9-amino-6-chloro-3-methyl-8-  
nitro-2,3,4,5-tetrahydro-1H-3-benzazepine in 100 ml. of  
glacial acetic acid is then added to the stirred diazonium  
solution dropwise during a period of 1 hour as the tem-  
perature is maintained at -10°C. Stirring is continued  
20 for 2 hours allowing the temperature to rise to 5°C.  
The solution is maintained at this temperature in a hood  
for 36 hours, then the solution is steam distilled to  
remove acetic acid. The residual liquid is cooled and  
sodium hydroxide is cautiously added with stirring. The  
25 crystalline 6-chloro-3-methyl-8-nitro-2,3,4,5-tetrahydro-  
1H-3-benzazepine is filtered. It may be purified by  
chromatography or recrystallization from ethyl acetate-  
hexane.

A stirred solution of 62 ml. of 0.9 M n-butyl  
30 lithium (0.056 mole) in tetrahydrofuran, under nitrogen,  
is cooled to -70°C. and a solution of 2.4 g. (0.01 mole)  
of 6-chloro-3-methyl-8-nitro-2,3,4,5-tetrahydro-1H-3-  
benzazepine in 25 ml. of tetrahydrofuran is added during a  
period of 30 minutes. The solution is stirred at -70°C.  
35 for 30 minutes and then a solution of 13.5 g. (0.06 mole)

1 of diphenyldisulfide in 40 ml. of tetrahydrofuran is added  
dropwise. After being stirred at  $-70^{\circ}\text{C}$ . for 1 hour the  
solution is poured into 500 ml. of ice/water containing  
excess hydrochloric acid. The mixture is extracted with  
5 ethyl acetate and then the aqueous phase is made alkaline  
with 10 N sodium hydroxide to precipitate 3-methyl-8-  
nitro-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.  
The product is filtered and recrystallized from ethyl  
acetate-hexane or aqueous ethanol.

10 Following the procedures outlined in Examples 9  
and 10, the 3-methyl-8-nitro-6-phenylthio-2,3,4,5-tetra-  
hydro-1H-3-benzazepine is reduced with sodium hydrosulfite  
and the corresponding 8-amino derivative is diazotized and  
then heated with cuprous sulfate/sulfuric acid to yield  
15 8-hydroxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine.

#### EXAMPLE 13

Following the procedures outlined in Example 12,  
9-amino-6-chloro-3-methyl-8-nitro-2,3,4,5-tetrahydro-1H-3-  
20 benzazepine is treated with n-butyl lithium followed by  
diphenyldisulfide to give the corresponding 6-phenylthio  
derivative which is diazotized and then reacted with  
cuprous chloride and hydrochloric acid to give 9-chloro-8-  
nitro-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
25 benzazepine. The latter is reduced with sodium  
hydrosulfite and the resulting 8-amino derivative is  
diazotized and then treated with cuprous sulfate/sulfuric  
acid to furnish 9-chloro-8-hydroxy-3-methyl-6-phenyl-  
thio-2,3,4,5-tetrahydro-1H-3-benzazepine.

#### EXAMPLE 14

30 The free base of 7,8-dimethoxy-3-methyl-2,3,4,5-  
tetrahydro-1H-3-benzazepine (0.075 mole) is dissolved in  
170 ml. of acetic acid. Bromine (28 g., 0.175 mole) is  
added in a thin stream and the mixture is stirred for 2  
35 hours. The precipitate is collected, washed with ether

1 and dissolved in boiling methanol and acetone to destroy  
excess bromine. The product, 6-bromo-7,8-dimethoxy-3-  
methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide,  
is allowed to crystallize from the methanol. The hydro-  
5 bromide is then converted to the corresponding free base.

A mixture of the 6-bromo compound (0.009 mole),  
trifluoromethyl iodide (0.036 mole) and 0.0708 mole of  
copper powder in 15 ml. of dimethylformamide in a pressure  
reactor is heated at 150°C. for 68 hours. The cooled  
10 reaction mixture is diluted with 20 ml. of dimethyl-  
formamide, 200 ml. of ethyl acetate and then stirred while  
500 ml. of water is added. The separated organic phase is  
washed, dried and evaporated to give 7,8-dimethoxy-3-  
methyl-6-trifluoromethyl-2,3,4,5-tetrahydro-1H-3-  
15 benzazepine which is demethylated in methylene chloride  
with boron tribromide.

Following the procedures outlined in Example 2  
the 7,8-dihydroxy-3-methyl-6-trifluoromethyl-2,3,4,5-  
tetrahydro-1H-3-benzazepine hydrobromide is treated with  
20 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to give the  
7,8-dione which is then reacted with, for example,  
thiophenol to yield 7,8-dihydroxy-3-methyl-6-phenylthio-9-  
trifluoromethyl-2,3,4,5-tetrahydro-1H-3-benzazepine  
hydrobromide.

25 Similar demethylation of the above prepared  
6-bromo compound followed by formation of the quinone and  
treatment with thiophenol furnishes 9-bromo-7,8-  
dihydroxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine, free base m.p. 174°C. (dec.).

30 EXAMPLE 15

To a stirred solution of 42.6 g. (0.206 mole) of  
7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine in 1 l.  
of toluene were added 35.7 ml. of triethylamine (0.256  
mole) and 24.5 ml. of ethyl chloroformate (0.256 mole), at  
35 room temperature, and the mixture was refluxed for 12

1 hours. The reaction mixture was filtered to remove  
triethylamine hydrochloride and the filtrate was concen-  
trated. The solid residue (57 g.) was recrystallized from  
ethyl acetate to give 3-carboethoxy-7,8-dimethoxy-2,3,4,5-  
5 tetrahydro-1H-3-benzazepine, m.p. 91-93°C.

The above prepared compound (57 g., 0.204 mole) was  
dissolved in 1 l. of carbon tetrachloride. The solution  
was cooled to -15°C. and, under a positive argon  
pressure, 34.2 ml. (0.306 mole) of benzene sulfonyl  
10 chloride were added dropwise with stirring. Anhydrous  
zinc chloride (22.5 g., 0.165 mole) was added all at once  
and the resulting mixture was stirred at room temperature  
for 12 hours. An additional 10 ml. of benzene sulfonyl  
chloride and 11 g. of zinc chloride were added and the  
15 mixture was stirred at room temperature for 24 hours. The  
reaction mixture was filtered, the filtrate was concen-  
trated and the resulting oil was chromatographed on a wet  
silica column. The product was eluted with increasing  
concentrations of ethyl acetate in hexane (20-50%) to give  
20 33.3 g. of 3-carboethoxy-7,8-dimethoxy-6-phenylthio-  
2,3,4,5-tetrahydro-1H-3-benzazepine.

To 700 ml. of tetrahydrofuran containing 12.9 g.  
(0.34 mole) of lithium aluminum hydride was added dropwise  
with stirring 32.9 g. (0.085 mole) of the above-prepared  
25 6-phenylthio compound dissolved in 400 ml. of tetrahydro-  
furan. After the addition was complete the mixture was  
refluxed for 3 hours and the excess hydride was quenched  
carefully by the addition of 12.9 ml. of water, 12.9 ml.  
of 20% sodium hydroxide solution and 38.7 ml. of water.  
30 The mixture was filtered and the inorganic solid was  
washed thoroughly with tetrahydrofuran. The filtrate was  
concentrated and the resulting oil was chromatographed on  
silica using methanol/chloroform to give 13 g. of  
7,8-dimethoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
35 benzazepine.



1           To a solution of 13 g. (0.04 mole) of  
7,8-dimethoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine in 750 ml. of methanol was added slowly with  
stirring at room temperature 316 ml. of a 0.5 M solution  
5 of sodium periodate. The reaction mixture was stirred in  
a water bath heated to 40°C. for 18 hours, filtered and  
the filtrate was concentrated. The residue was  
partitioned between chloroform and water, and the aqueous  
layer was extracted with chloroform. The combined extract  
10 was dried over sodium sulfate and evaporated in vacuo to  
yield 10.4 g. of oil which was triturated with ether to  
furnish 8.3 g. of solid 7,8-dimethoxy-3-methyl-6-phenyl-  
sulfinyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p.  
128-132°C.

15           The above-prepared sulfoxide (8.3 g., 0.024 mole)  
was dissolved in 200 ml. of methylene chloride. The  
solution was cooled to -78°C. and, under argon, a  
solution of 7.9 ml. (0.108 mole) of thionyl chloride in 75  
ml. of methylene chloride was added dropwise. The mixture  
20 was stirred in the cold for four hours and gradually  
allowed to warm to room temperature. The reaction mixture  
was concentrated and the resulting oil was washed with 10%  
sodium hydroxide solution, then extracted into chloro-  
form. The dried extract was evaporated in vacuo and the  
25 residue was chromatographed on silica using methanol/  
chloroform to give 4.8 g. of 9-chloro-7,8-dimethoxy-3-  
methyl-6-phenyl-thio-2,3,4,5-tetrahydro-1H-3-benzazepine;  
hydrochloride salt m.p. 209-210°C.

To a solution of the above 9-chloro compound  
30 (3.76 g., 0.0104 mole) in 120 ml. of methanesulfonic acid  
was added 1-methionine (8.6 g., 0.058 mole). The mixture  
was stirred at room temperature for 18 hours, quenched  
with ice/water and made basic with concentrated ammonium  
hydroxide to pH 9.5. The resulting mixture was extracted  
35 with ethyl acetate and the extract was dried over sodium

- 1 sulfate. Evaporation of the ethyl acetate yielded 1.8 g.  
(52% crude yield) of 9-chloro-7,8-dihydroxy-3-methyl-6-  
phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p.  
174-176°C., identical to the material prepared in Example  
5 6 above.

#### EXAMPLE 16

- A mixture of 2.6 g. (0.008 mole) of 7,8-dimethoxy-3-  
methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine  
(prepared as in Example 3) and 1.26 g. (0.0085 mole) of  
10 dl-methionine in 35 ml. of methanesulfonic acid was stirred  
at room temperature for 3.5 hours. The reaction mixture was  
quenched with ice/water, made basic with 10% sodium  
hydroxide solution to pH 8.5 and extracted with chloroform.  
The extract was washed with saturated sodium chloride  
15 solution, dried over sodium sulfate and evaporated to give  
2.18 g. (87% yield) of 8-hydroxy-7-methoxy-3-methyl-6-phenyl-  
thio-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 161-162°C.

- Reaction of 8-hydroxy-7-methoxy-3-methyl-6-phenyl-  
thio-2,3,4,5-tetrahydro-1H-3-benzazepine with acetyl bromide  
20 in trifluoroacetic acid gave 8-acetoxy-7-methoxy-3-methyl-6-  
phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine; hydro-  
chloride salt m.p. 240-241°C.

#### EXAMPLE 17

- As above.  
To a solution of 1.0 g. (0.0078 mole) of  
25 p-fluorothiophenol in 200 ml. of methanol was added  
portionwise 2 g. (0.0073 mole) of 3-methyl-2,3,4,5-tetra-  
hydro-1H-3-benzazepine-7,8-dione hydrobromide (prepared as  
in Example 2) and the resulting mixture was stirred at room  
temperature under argon for 1 hour. The methanol was  
30 distilled from the reaction mixture in vacuo and the residue  
was partitioned between ether and water. The aqueous layer  
was extracted with ether and then made basic with ammonium  
hydroxide solution. The precipitate was filtered and the  
dried filtrate was chromatographed on silica using methanol/  
35 chloroform. The material eluted from the column was slurried

1 with ether and filtered. Distillation of the ether gave  
7,8-dihydroxy-6-(p-fluorophenylthio)-3-methyl-2,3,4,5-tetra-  
hydro-1H-3-benzazepine, m.p. 164-166°C.

Similarly, reaction of 1 g. (0.0075 mole) of  
5 p-toluenethiol and 2 g. of the dione in 200 ml. of methanol  
as described above gave 7,8-dihydroxy-3-methyl-6-(p-tolyl-  
thio)-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 105-114°C  
and reaction of 1.65 g. (0.0011 mole) of p-nitrothiophenol  
and 2.3 g. of the dione in 200 ml. of methanol gave 7,8-di-  
10 hydroxy-3-methyl-6-(p-nitrophenylthio)-2,3,4,5-tetrahydro-1H-  
3-benzazepine, m.p. 165-170°C.

Reaction of 7,8-dihydroxy-6-(p-fluorophenylthio)-3-  
methyl-2,3,4,5-tetrahydro-1H-3-benzazepine with acetyl bro-  
mide as described in Example 4 yielded 7,8-diacetoxy-6-(p-  
15 fluorophenylthio)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzaze-  
pine, m.p. 125-127°C.

#### EXAMPLE 18

Following the procedures outlined in Example 17,  
0.9 g. (0.0075 mole) of furfuryl mercaptan and 2 g. (0.0073  
20 mole) of 3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-  
dione hydrobromide were reacted in 200 ml. of methanol to  
yield 7,8-dihydroxy-6-furfurylthio-3-methyl-2,3,4,5-tetra-  
hydro-1H-3-benzazepine, free base m.p. 162-165°C.

#### EXAMPLE 19

25 To a solution of 1.3 g. (0.02 mole) of potassium  
hydroxide in 20 ml. of water was added 2.9 g. (0.022 mole)  
of p-fluorothiophenol in 20 ml. of ethanol. The mixture was  
refluxed for 1 hour and 4.8 g. (0.02 mole) of 6-chloro-3-  
methyl-9-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine (prepared  
30 as in Example 9) in 20 ml. of ethanol was added. The  
resulting solution was refluxed for 4.5 hours and allowed to  
cool. A red oil was decanted from the reaction mixture,  
dissolved in ethyl acetate and washed with saturated sodium  
chloride solution and 10% sodium hydroxide solution. The  
35 dried ethyl acetate solution was evaporated to give 5.3 g.  
of 6-(p-fluorophenylthio)-3-methyl-9-nitro-2,3,4,5-tetra-  
hydro-1H-3-benzazepine.

1 A mixture of 4.3 g. (0.0135 mole) of the above  
prepared 9-nitro derivative dissolved in 100 ml. of ethanol,  
50 ml. of 1 N sulfuric acid and 0.4 g. of 5% palladium-on-  
carbon in 50 ml. of ethanol was hydrogenated at 60 p.s.i.  
5 for 2 hours. The catalyst was filtered from the reaction  
mixture and the filtrate was evaporated. The residue was  
dissolved in a minimum amount of ethanol to which ethereal  
hydrogen chloride was added. The solid was filtered to give  
1.5 g. of 9-amino-6-(p-fluorophenylthio)-3-methyl-  
10 2,3,4,5-tetrahydro-1H-3-benzazepine dihydrochloride.

Following the procedure outlined in Example 9, the  
9-amino-3-benzazepine dihydrochloride (1.25 g.) was  
diazotized with sodium nitrite in water and concentrated  
hydrochloric acid and then treated with cuprous chloride to  
15 yield, after purification on silica, 9-chloro-6-(p-fluoro-  
phenylthio)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;  
hydrochloride salt m.p. 212-213°C.

#### EXAMPLE 20

To a solution of 34 g. (0.177 mole) of 7,8-di-  
20 methoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine in 200  
ml. of trifluoroacetic acid was added 40 ml. of bromine (118  
g., 0.735 mole) in 200 ml. of acetic acid and the solution  
was refluxed for 2 hours on a steam bath. The reaction  
mixture was quenched with 40% sodium hydroxide solution to  
25 pH 8 and then extracted with ethyl acetate. The extract was  
washed with water, dried and evaporated to leave  
6,9-dibromo-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-  
3-benzazepine; hydrochloride salt m.p. 219-220°C.

A sample of 9.7 g. (0.0256 mole) of the above  
30 6,9-dibromo compound was evaporated three times from dry  
methylene chloride. After being dried with magnesium  
sulfate, the methylene chloride solution was evaporated and  
the residue was dissolved in 200 ml. of dry toluene. The  
solution was stirred under argon at -78°C. and 9.82 ml.  
35 (0.0256 mole) of fresh n-butyl lithium solution in hexane

1 was added. To the resulting cold solution was added 20 g.  
(0.0917 mole) of diphenyl disulfide and the mixture was  
stirred for 1 hour. The reaction mixture was quenched with  
10% hydrochloric acid and extracted with ether. The aqueous  
5 solution was made basic and extracted with ethyl acetate.  
The extract was washed with water, dried and evaporated to  
give 6.3 g. of crude oil which was chromatographed on silica  
with ethyl acetate. The resulting oil was passed quickly  
through a column containing alumina with ethyl acetate and  
10 the solution was evaporated. The residue was taken into  
ether and treated with ethereal hydrogen chloride to give  
9-bromo-7,8-dimethoxy-3-methyl-6-phenylthio-2,3,4,5-  
tetrahydro-1H-3-benzazepine hydrochloride, m.p. 201-203°C.

A mixture of 1.03 g. (0.0023 mole) of the above  
15 prepared hydrochloride, 100 ml. of methanesulfonic acid, 5  
ml. of water and 4 g. (0.027 mole) of methionine was stirred  
at room temperature for 72 hours. The reaction mixture was  
poured onto ice, made basic with ammonium hydroxide solution  
to pH 7 and extracted with ethyl acetate. The extract was  
20 washed with aqueous sodium bisulfite and water, dried and  
evaporated to yield 600 mg. of 9-bromo-7,8-dihydroxy-3-  
methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine,  
m.p. 174°C. (dec.).

#### EXAMPLE 21

25 To a solution of 1.1 g. (0.0011 mole) of  
2-furanthiol in 200 ml. of methanol is added portionwise 2.3  
g. (0.0084 mole) of 3-methyl-2,3,4,5-tetrahydro-1H-3-benza-  
zepine-7,8-dione hydrobromide. After stirring for 1 hour at  
room temperature the reaction mixture is filtered and the  
30 filtrate concentrated in vacuo to give 7,8-dihydroxy-6-  
(2-furylthio)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine  
hydrobromide.

Similarly reaction of 1.44 g. (0.0011 mole) of  
2-thiophenemethanethiol in 200 ml. of methanol and the above  
35 dione (2.3 g., 0.0084 mole) gives 7,8-dihydroxy-3-methyl-6-  
(2-thienylmethylthio)-2,3,4,5-tetrahydro-1H-3-benzazepine  
hydrobromide.

1

EXAMPLE 22

To a solution of 12.8 g. (0.052 mole) of 7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (prepared as in Example 1) in 50 ml. of glacial acetic acid at 55°C. was added 3.0 ml. of bromine (8.8 g., 0.055 mole) dropwise over 1 hour with stirring. After addition was completed, the temperature was raised to 70°C. for 2 hours. The reaction mixture was poured into ice/water and made basic with 40% sodium hydroxide solution. The basic solution was extracted with ethyl acetate and the extract dried over sodium sulfate. Removal of the solvent gave 6-bromo-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine as an oil.

A solution of 1.0 g. (0.0035 mole) of the 6-bromo compound prepared above in 20 ml. of dry tetrahydrofuran was added to 2.0 ml. of a 2.3 M solution of n-butyl lithium in hexane at -78°C. under argon over a 1 hour period. The mixture was stirred for an additional 30 minutes and then 2.9 g. (0.0079 mole) of diphenyl disulfide in 10 ml. of tetrahydrofuran was added dropwise. This mixture was stirred at -78°C. for 2 hours, allowed to stand at room temperature for 18 hours and then slowly poured into a mixture of ice/water (50 ml.) and ether (25 ml.). The aqueous layer was extracted with ether, and the ether extract was extracted with 3 N hydrochloric acid. The acid layer was made basic with sodium hydroxide solution and extracted with ethyl acetate. The dried extract was concentrated to dryness to leave 7,8-dimethoxy-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

Ethylene oxide (0.5 ml., 0.44 g., 0.010 mole) is added to a stirred solution of 1.58 g. (0.005 mole) of 7,8-dimethoxy-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine in 100 ml. of methanol at 0°C. The mixture is stirred at this temperature for 2 hours and then allowed to warm to room temperature. Concentration of the mixture in vacuo gives 7,8-dimethoxy-3-(2-hydroxyethyl)-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

1           The above prepared benzazepine (1.66 g., 0.005  
mole) is refluxed in 25 ml. of 48% hydrobromic acid for 2  
hours. The reaction mixture is evaporated to dryness in  
vacuo and the residue distilled azeotropically with toluene  
5 to leave the product, 7,8-dihydroxy-3-(2-hydroxyethyl)-6-  
phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide.

EXAMPLE 23

To a solution of 1.58 g. (0.005 mole) of 7,8-  
dimethoxy-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine  
10 in 25 ml. of methylene chloride and 1.0 g. of triethylamine  
is added dropwise 1.05 g. (0.010 mole) of cyclopropane-  
carboxylic acid chloride at 5°C. and the mixture is  
stirred at room temperature for 3 hours. The reaction  
mixture is filtered and the filtrate is washed with water,  
15 5% potassium carbonate solution and then with water, dried  
and subsequently concentrated to give 3-cyclopropane-  
carbonyl-7,8-dimethoxy-6-phenylthio-2,3,4,5-tetrahydro-1H-  
3-benzazepine.

The cyclopropanecarbonyl derivative (1.85 g., 0.005  
20 mole) in 10 ml. of dry tetrahydrofuran is added to 20 ml. of  
a 1.02 M solution of diborane in tetrahydrofuran (0.02 mole)  
at 0°C. and under argon. The mixture is allowed to come  
to room temperature and then refluxed for 3 hours. The  
cooled reaction mixture is treated with methanol and 3 N  
25 hydrochloric acid to decompose excess diborane and refluxed  
for 1 hour. This mixture is evaporated to dryness and the  
residue is taken up into water, then extracted with ether.  
The aqueous layer is made basic with sodium hydroxide  
solution, extracted with methylene chloride, dried and  
30 concentrated to leave 3-cyclopropylmethyl-7,8-  
dimethoxy-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.  
Demethylation with 48% hydrobromic acid as described in  
Example 24 yields 3-cyclopropylmethyl-7,8-dihydroxy-6-  
phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide.

1

EXAMPLE 24

To a solution of 1.58 g. (0.005 mole) of 7,8-dimethoxy-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine in 25 ml. of methylene chloride and 1.0 g. of triethylamine is added dropwise 1.85 g. (0.010 mole) of 2-phenethylbromide at 5°C. The mixture is stirred at room temperature for 3 hours, filtered and the filtrate is washed with water, then extracted with dilute hydrochloric acid. The acid extract is washed with ether and made basic with 10% sodium hydroxide solution to give the product 7,8-dimethoxy-3-(2-phenethyl)-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine. Demethylation with 48% hydrobromic acid as described in Example 24 yields 7,8-dihydroxy-3-(2-phenethyl)-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide.

EXAMPLE 25

A solution of 5.0 g. (0.0396 mole) of m-fluoroanisole in 44 ml. of dry tetrahydrofuran was treated with 14.5 ml. of 2.6 M solution of n-butyl lithium in hexane at -65°C., and the resulting mixture was stirred in the cold for 2-1/4 hours. Trimethylborate ester (6.41 g., 0.0377 mole) in 52 ml. of dry ether was added at -65°C. over a 15 minute period. The reaction mixture was allowed to warm to room temperature, and dilute hydrochloric acid was added. The organic layer was separated, washed with water, dried and concentrated to give 3-fluoro-2-(dihydroxyborinyl)anisole (4.62 g., 80% yield).

To a solution of the above prepared anisole (4.55 g., 0.0268 mole) in 33 ml. of warm toluene was added slowly 12.4 ml. of 30% hydrogen peroxide solution, and the mixture was heated on a steam bath for 45 minutes. The reaction mixture was cooled, and the separated organic layer was washed with water, 10% ferrous ammonium sulfate solution and water. The organic solution was then extracted with 10% sodium hydroxide solution, and the basic extract was made



1 acid with concentrated hydrochloric acid to give an oil.  
The oil was extracted with methylene chloride, dried and  
concentrated to leave 3-fluoro-2-hydroxyanisole (2.04 g.,  
69% yield).

5 The hydroxyanisole derivative (1.77 g., 0.0125  
mole) was dissolved in 18 ml. of dry acetone, and 3.44 g. of  
powdered potassium carbonate and 2.36 ml. of methyl sulfate  
were added. The mixture was stirred and refluxed for 30  
10 minutes, diluted with water and extracted with ether. The  
ether extract was washed with water, stirred for 90 minutes  
with dilute ammonium hydroxide solution, and the separated  
organic layer was washed with water. The dried organic  
solution was concentrated to 1.64 g. (68% yield) of liquid,  
3-fluoro-2-methoxyanisole, b.p. 93.5-102°C. at 19-24 mm.  
15 of mercury pressure.

A solution of 37% formaldehyde (25 ml.) was added  
to a solution of the above prepared methoxyanisole (25.0 g.,  
0.16 mole) in 100 ml. of glacial acetic acid and hydrogen  
chloride gas was bubbled in for 4-1/2 hours. The tempera-  
20 ture was maintained at 20-25°C. by means of an ice/water  
bath. The reaction mixture was poured into water, extracted  
with ether and the ether extract washed with water. The  
dried extract was concentrated at 35°C. to leave 31.63 g.  
(97% yield) of 3,4-dimethoxy-2-fluorobenzyl chloride, m.p.  
25 44.5-47.5 °C.

Sodium cyanide (9.19 g., 0.187 mole) was added to a  
solution of the above benzyl chloride (30.7 g., 0.15 mole)  
in 530 ml. of dimethyl sulfoxide. After about 45 minutes,  
the reaction mixture was poured into 1 l. ice/water and  
30 extracted with ether. The ether extract was washed with  
water, dried and concentrated at 50°C. to give 26.9 g.  
(92% yield) of 3,4-dimethoxy-2-fluorobenzyl nitrile.

The benzyl nitrile (3.9 g., 0.02 mole) was  
dissolved in equal volumes of ethanol and 10 N aqueous  
35 sodium hydroxide (50 ml. of each) and refluxed for 24

1 hours. The reaction mixture was poured into about 200 ml.  
of hot water, filtered, and the hot filtrate was acidified  
with concentrated hydrochloric acid. Cooling yielded  
2-fluorohomoveratric acid.

5 Following the procedures outlined in Examples 1 and  
2, the 2-fluorohomoveratric acid is reacted with amino-  
acetaldehyde dimethylacetal to form N-(2,2-dimethoxyethyl)-  
3,4,-dimethoxy-2-fluorophenylacetamide which is ring closed  
with hydrochloric acid and glacial acetic acid to obtain  
10 2,3-dihydro-7,8-dimethoxy-6-fluoro-2-oxo-1H-3-benzazepine.  
The dihydrobenzazepine is reduced first with hydrogen and  
palladium-on-carbon, then with diborane to give  
7,8-dimethoxy-6-fluoro-2,3,4,5-tetrahydro-1H-3-benzazepine.  
The latter is treated with formaldehyde/formic acid to give  
15 the corresponding 3-methyl derivative which is demethylated  
with 48% hydrobromic acid. The resulting catechol is  
oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and  
the dione is treated with a methanolic solution of  
thiophenol to furnish the product 7,8-dihydroxy-9-fluoro-3-  
20 methyl-6-phenyl-thio-2,3,4,5-tetrahydro-1H-3-benzazepine.

#### EXAMPLE 26

Following the procedures outlined in Example 2, a  
methanolic solution of p-methoxythiophenol is reacted with  
3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-dione  
25 hydrobromide to yield the product, as the free base,  
7,8-dihydroxy-6-(p-methoxyphenylthio)-3-methyl-2,3,4,5-tetra-  
hydro-1H-3-benzazepine. Treatment with boron tribromide in  
methylene chloride solution gives 7,8-dihydroxy-6-(p-hydroxy-  
phenylthio)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

#### EXAMPLE 27

30 To a solution of 18.21 g. (0.0446 mole) of 9-bromo-  
7,8-dimethoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine (prepared as in Example 20) in 200 ml. of  
toluene, cooled to -78°C., is slowly added 26.0 ml. of 2.1  
35 M n-butyl lithium in hexane. After 20 minutes at this

1 temperature 23.1 ml. of dimethylformamide is added and the  
mixture is stirred for 1/2 hour. The reaction mixture, at  
room temperature, is poured into 10% sodium hydroxide  
solution and extracted with ethyl acetate. The extract is  
5 washed with water, dried and concentrated to give  
7,8-dimethoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine-9-carboxaldehyde.

The aldehyde (10.72 g., 0.03 mole) is dissolved in  
50 ml. of methanol and 3.42 g. (0.09 mole) of sodium boro-  
10 hydride is added slowly. The mixture is stirred for 1 hour,  
quenched with acetic acid, evaporated, made basic and  
extracted with ethyl acetate. The extract is washed with  
water, dried and evaporated to leave 7,8-dimethoxy-9-hydroxy-  
methyl-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
15 benzazepine.

A mixture of 5.39 g. (0.015 mole) of the above  
9-hydroxymethyl derivative in 100 ml. of chloroform and 75  
ml. of concentrated hydrochloric acid is refluxed for 2  
hours. The reaction mixture is evaporated and partitioned  
20 between hydrochloric acid and ethyl acetate. The acid  
solution is made basic with 40% sodium hydroxide solution  
and extracted with ethyl acetate. The extract is washed  
with water, dried and evaporated to give 9-chloromethyl-  
7,8-dimethoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
25 benzazepine.

To a solution of 3.77 g. (0.01 mole) of the  
9-chloromethyl derivative is added slowly 1.4 g (0.036 mole)  
of sodium borohydride and the mixture is heated on a steam  
bath under argon for 3 hours. The reaction mixture is  
30 extracted with aqueous ethyl acetate, and the extract is  
washed with water. The dried extract is then evaporated to  
yield 7,8-dimethoxy-3,9-dimethyl-6-phenylthio-2,3,4,5-tetra-  
hydro-1H-3-benzazepine.

A solution of 1.717 g. (0.,005 mole) of the  
35 9-methyl benzazepine in ethyl acetate is treated with

1 ethereal hydrogen chloride and then evaporated. The residue  
is dissolved in 25 ml. of dry methylene chloride, cooled to  
0°C. and 9.23 ml. of a solution of 1 g. of boron  
tribromide per 2.5 ml. of methylene chloride (0.015 mole) is  
5 added. After 10 minutes the reaction mixture is evaporated  
and the residue extracted with ethyl acetate/water/ammonium  
hydroxide. The ethyl acetate extract is washed with water,  
dried and evaporated to give 7,8-dihydroxy-3,9-dimethyl-6-  
phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

10

EXAMPLE 28

To a solution of 0.8 g. (0.0022 mole) of 9-chloro-  
7,8-dimethoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-  
3-benzazepine (prepared as in Example 15) in 10 ml. of  
methylsulfonic acid at room temperature is added 0.35 g.  
15 (0.0023 mole) of solid methionine all at once and the mix-  
ture is stirred for 4 hours. The reaction mixture is  
quenched in ice/water and made basic (pH 7.5) with concen-  
trated ammonium hydroxide. The basic solution is extract-  
ed with methylene chloride and washed with saturated sodium  
20 chloride solution. The organic layer is dried and  
evaporated in vacuo to leave 9-chloro-8-hydroxy-7-methoxy-  
3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

EXAMPLE 29

A mixture of 0.45 g. (0.0013 mole) of 9-chloro-8-  
25 hydroxy-7-methoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-  
1H-3-benzazepine and 0.2 ml. (0.0026 mole) of acetyl bromide  
in trifluoroacetic acid is heated to reflux on a steam bath  
for 2 hours. The reaction mixture is concentrated and the  
residue is taken up in 100 ml. of methylene chloride. This  
30 solution is dried and evaporated to give 8-acetoxy-9-chloro-  
7-methoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-  
benzazepine.

1

EXAMPLE 30

	<u>Ingredients</u>	<u>Mg. per Capsule</u>
	7,8-dihydroxy-6-phenylthio 2,3,4,5-tetrahydro-1H-3-	50 (free base)
5	benzazepine (as an acid addition salt)	
	Magnesium stearate	2
	Lactose	200
10	The above ingredients are mixed, passed through a #40 mesh screen, remixed and filled into #2 capsules.	

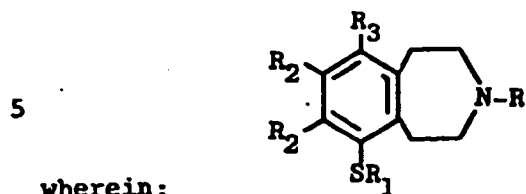
EXAMPLE 31

	<u>Ingredients</u>	<u>Mg. per Tablet</u>
15	7,8-dihydroxy-3-methyl-6- phenylthio-2,3,4,5- tetrahydro-1H-3- benzazepine (as an acid addition salt)	10
	Calcium sulfate, dihydrate	150
20	Sucrose	25
	Starch	15
	Talc	5
	Stearic acid	3
25	The sucrose, calcium sulfate and active ingredient are thoroughly mixed and granulated with hot 10% gelatin solution. The wetted mass is passed through a #6 mesh screen directly onto drying trays. The granules are dried at 50°C. and passed through a #20 mesh screen, mixed 30 with the starch, talc and stearic acid, and compressed into tablets.	

The capsules or tablets prepared as in Examples 30 and 31 are administered internally to an animal or human subject requiring antipsychotic or antiemetic therapy within the dose ranges set forth hereinabove. Similarly other compounds of formula I can be formulated in the same manner to give pharmaceutical compositions useful in producing dopamine receptor blocking activity.

1 We claim:

1. A compound represented by the formula:



R is methyl, allyl, dimethylallyl, phenethyl, cyclopropylmethyl or  $\beta$ -hydroxyethyl;

10  $R_1$  is phenyl, m- or p-substituted phenyl with the substituent being trifluoromethyl, chloro, methoxy, methyl, fluoro, nitro or hydroxy, cyclohexyl, thienyl, thienylmethyl, furyl or furylmethyl;

$R_2$  is hydrogen, methoxy, alkanoyloxy with the  
15 alkanoyl moiety having from 2 to 6 carbon atoms, or hydroxy, each  $R_2$  being the same or different except that when one of  $R_2$  is alkanoyloxy the other is hydrogen, methoxy or alkanoyloxy; and

$R_3$  is hydrogen, chloro, bromo, trifluoromethyl,  
20 fluoro or methyl,

or a nontoxic pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1 in which R is methyl,  $R_1$  is phenyl, p-trifluoromethylphenyl, p-chloro-  
25 phenyl, p-tolyl, p-fluorophenyl, cyclohexyl or 2-thienyl, both  $R_2$  are hydrogen, acetoxy or hydroxy, or one  $R_2$  is hydroxy and the other is methoxy, and  $R_3$  is hydrogen, chloro or bromo.

3. A compound according to claim 2 in which both  
30  $R_2$  are hydroxy.

4. A compound according to claim 3 being the compound 7,8-dihydroxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

5. A compound according to claim 3 being the  
35 compound 9-chloro-7,8-dihydroxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

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1 6. A compound according to claim 3 being the compound 7,8-dihydroxy-3-methyl-6-(2-thienylthio)-2,3,4,5-tetrahydro-1H-3-benzazepine.

5 7. A compound according to claim 3 being the compound 6-(p-fluorophenylthio)-7,8-dihydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

8. A compound according to claim 3 being the compound 9-bromo-7,8-dihydroxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

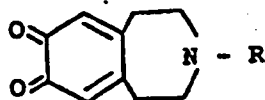
10 9. A compound according to claim 2 in which both  $R_2$  are hydrogen.

10. A compound according to claim 9 being the compound 3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

15 11. A compound according to claim 2 being the compound 8-hydroxy-7-methoxy-3-methyl-6-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepine.

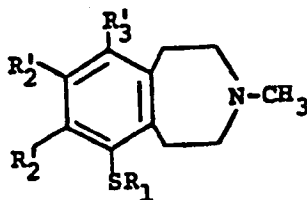
12. A compound represented by the formula:

20



13. A process for the preparation of a  
25 compound represented by the formula:

30

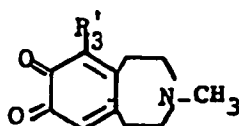


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- 1 wherein  $R_1$  is phenyl, m- or p-substituted phenyl with the  
substituent being trifluoromethyl, chloro, methoxy, methyl,  
fluoro, nitro or hydroxy, cyclohexyl, thienyl, thienyl-  
methyl, furyl or furylmethyl; both  $R_2$  are methoxy, alkanoy-  
5 loxy with the alkanoyl moiety having from 2 to 6 carbon  
atoms, or hydroxy; and  $R_3$  is hydrogen, bromo, fluoro or  
trifluoromethyl; or a nontoxic pharmaceutically acceptable  
acid addition salt thereof, which comprises reacting a  
dione represented by the formula:

10



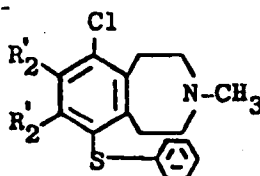
15

- wherein  $R_3$  is as defined above, with a mercaptan,  $R_1SH$ ,  
in which  $R_1$  is as defined above except for hydroxy sub-  
stituted phenyl; optionally treating a methoxy substituted  
phenyl product with boron tribromide to give the correspond-  
20 ing hydroxy substituted derivative; optionally reacting the  
7,8-dihydroxy product with diazomethane or an alkanoyl  
halide to give the corresponding dimethoxy or dialkanoyloxy  
derivative, respectively; and optionally forming an acid  
addition salt of the compound obtained as above.

25

14. A process for the preparation of a compound  
represented by the formula:

30



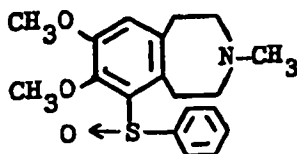
- wherein both  $R_2$  are methoxy, alkanoyloxy with the alkanoyl  
moiety having from 2 to 6 carbon atoms, or hydroxy; or a  
35 nontoxic pharmaceutically acceptable acid addition salt



- 40 -

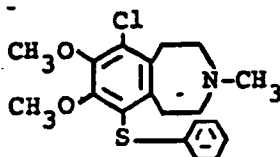
1 thereof; which comprises treating a compound represented  
by the formula:

5



with thionyl chloride to give the following compound:

10

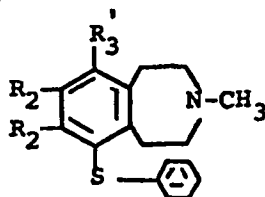


15

; optionally demethylating the methoxy groups; optionally  
reacting the 7,8-dihydroxy product with an alkanoyl halide  
to give the corresponding dialkanoyloxy derivative; and  
optionally forming an acid addition salt of the compound  
20 obtained as above.

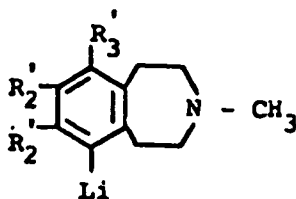
15. A process for the preparation of a compound  
represented by the formula:

25



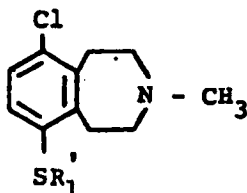
wherein both  $R_2$  are hydrogen, methoxy, alkanoyloxy with the  
30 alkanoyl moiety having from 2 to 6 carbon atoms, or  
hydroxy and  $R_3$  is hydrogen or bromo, or a nontoxic pharma-  
ceutically acceptable acid addition salt thereof, which  
comprises reacting a compound represented by the formula:

35

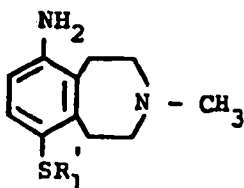


wherein both  $R_2$  are hydrogen or methoxy and  $R_3$  is hydrogen or bromo, with diphenyldisulfide; optionally demethylating the methoxy groups; optionally reacting the 7,8-dihydroxy product with an alkanoyl halide to give the corresponding dialkanoyloxy derivative; and optionally forming an acid addition salt of the compound obtained as above.

16. A process for the preparation of a compound represented by the formula:



wherein  $R_1$  is phenyl, m- or p-substituted phenyl with the substituent being trifluoromethyl, chloro, methoxy, methyl, fluoro or hydroxy, cyclohexyl, thienyl, thienylmethyl, furyl or furylmethyl, or a nontoxic pharmaceutically acceptable acid addition salt thereof, which comprises diazotizing an amino compound represented by the formula:



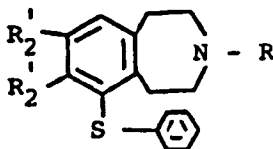
wherein  $R_1$  is as defined above except for hydroxy substituted phenyl, and reacting the resulting diazonium salt

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1 with cuprous chloride; optionally treating a methoxy substituted phenyl product with boron tribromide to give the corresponding hydroxy substituted derivative; and optionally forming an acid addition salt of the compound obtained  
5 as above.

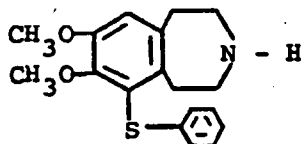
17. A process for the preparation of a compound represented by the formula:

10



wherein R is methyl, allyl, dimethylallyl, phenethyl, 15cyclopropylmethyl or  $\beta$ -hydroxyethyl; and both  $R_2$  are methoxy, alkanoyloxy with the alkanoyl moiety having from 2 to 6 carbon atoms, or hydroxy; or a nontoxic pharmaceutically acceptable acid addition salt thereof; which comprises N-alkylating or N-acylating a compound represented  
20 by the formula:

25

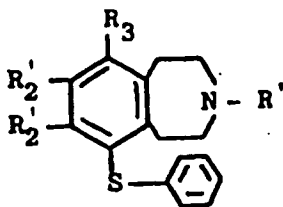


by reaction with,

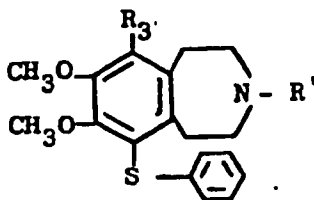
- a) formaldehyde and formic acid,
- b) allyl, dimethylallyl or 2-phenethyl bromide,
- 30 c) ethylene oxide or
- d) cyclopropanecarboxylic acid chloride

followed by reduction of the N-amide with diborane; optionally demethylating the methoxy groups; optionally reacting the 7,8-dihydroxy product with an alkanoyl halide  
35 to give the corresponding dialkanoyloxy derivative; and optionally forming an acid addition salt of the compound obtained as above.

- 1 18. A process for the preparation of a compound  
represented by the formula:



- wherein R' is methyl, allyl, dimethylallyl, phenethyl  
10 or cyclopropylmethyl; R<sub>2</sub> are both hydroxy or alkanoyloxy  
with the alkanoyl moiety having from 2 to 6 carbon atoms;  
and R<sub>3</sub> is hydrogen, chloro, bromo, trifluoromethyl or  
methyl; or a nontoxic pharmaceutically acceptable acid  
addition salt thereof, which comprises demethylating a  
15 compound represented by the formula:



- wherein R' and R<sub>3</sub> are as defined above; optionally reacting  
the 7,8-dihydroxy product with an alkanoyl halide to give  
the corresponding dialkanoyloxy derivative; and optionally  
25 forming an acid addition salt of the compound obtained  
as above.

19. A pharmaceutical composition having dopamine  
receptor blocking activity in dosage unit form comprising  
a pharmaceutical carrier and a nontoxic amount sufficient  
30 to produce said activity of a compound of claims 1, 4, 5,  
6, 7, 8, 10 or 11, or a pharmaceutically acceptable acid  
addition salt of said compound.



European Patent  
Office

# EUROPEAN SEARCH REPORT

Application number

EP 79 102 279.1

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A, P	DE - A1 - 2 804 285 (SMITHKLINE) —		C 07 D 223/16 A 61 K 31/55
A, P	US - A - 4 108 989 (SMITHKLINE) —		C 07 D 223/14
A	GB - A - 1 268 243 (WALLACE & TIERNAN) —		
D	US - A- 3 671 519 (AMERICAN HOME) —		TECHNICAL FIELDS SEARCHED (Int. Cl.)
D	US - A- 3 483 185 (AMERICAN HOME) —		A 61 K 31/55 C 07 D 223/14 C 07 D 223/16
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			
Place of search Berlin		Date of completion of the search 23-10-1979	Examiner KAPTEYN

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